ASSOCIATION OF METABOLIC SYNDROME WITH VITAMIN D

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Abstract

Metabolic syndrome and its complications – heart attacks, strokes, diabetes, cancer, degenerative diseases of the musculoskeletal system lead to the greatest number of deaths and disability than all other causes combined in developed countries.

The pathogenesis of metabolic syndrome is based on: cellular inflammation, inflammation of the endothelium of arteries, impaired microcirculation, liver, intestine, kidney disfunction, visceral obesity of these organs, chronic mental stress. Simply put – a violation of normal metabolism, which begins with cellular inflammation and develops into generalized inflammation of the body with a total disruption of normal structures and functions of human organs.

In this article, we investigated the association between metabolic syndrome, various links in its pathogenesis, and vitamin D levels based on literature overview. We also provided the results of our own practical studies of effective correction of metabolic syndrome indicators by optimizing vitamin D levels.

Keywords: metabolic syndrome, vitamin D, cardiovascular risk, diabetes mellitus, obesity, insulin resistance.

Introduction

The prevalence of the metabolic syndrome is increasing in developed and developing Countries. Metabolic syndrome is constellation of disturbances including glucose intolerance, central obesity, hypertension and dyslipidemia (hypertriglyceridemia, elevated non-esterified fatty acids and decreased high density lipoprotein cholesterol) present in several forms, depending upon the combination of the different components of the syndrome. It is well accepted that the metabolic syndrome increases the risk for the development of cardiovascular disease, type 2 diabetes, stroke and cancer (1).

Several explanations have been proposed to explain the origin of the metabolic syndrome. Some consider an initial insulin resistant state progressing to the other components, while others are of view that obesity is the main initiator of the syndrome (2).

More recently, the chronic low-grade inflammatory condition that often accompanies the metabolic syndrome has been implicated as a major factor both in the installation of the metabolic syndrome and its associated pathophysiological consequences (3).

However, the inflammatory state that accompanies the metabolic syndrome does not completely fit into the classical definition of acute or chronic inflammation, as it is not accompanied by infection; there is no massive tissue injury and the dimension of the inflammatory activation is also not large. So it is often called 'low grade' chronic inflammation or 'meta-inflammation', meaning metabolically-triggered inflammation (4) or even 'para-inflammation' an intermediate state between basal and inflammatory states (5).

Several studies support to the concept that a proinflammatory state is a component of the metabolic syndrome because of the strong association of elevated C-reactive protein (CRP) with metabolic syndrome risk factors and high CRP levels impart risk for major coronary events beyond that imparted by the other metabolic risk factors. High-sensitivity CRP (hs-CRP) has been developed and used as a marker to predict coronary vascular diseases in metabolic syndrome and it was recently used as a predictor for non-alcoholic fatty liver disease in correlation with serum markers that indicated lipid and glucose metabolism. Adipose tissue in obese persons with the metabolic syndrome releases increased amounts of cytokines into the circulation which in turn accounts for a greater production of CRP by the liver. Another possibility is that insulin resistance per se is responsible for a higher production of cytokines. Regardless of mechanism, the finding that patients with metabolic syndrome exhibit characteristics of a proinflammatory state provides a new and exciting connection between inflammation and metabolic processes. This connection promises to yield new insights into pathways whereby the metabolic syndrome leads to atherosclerosis and acute coronary syndromes (6).

Cellular inflammation and metabolic syndrome

Adipokines

Subcutaneous adipose tissue (SAT) makes up 80% of adipose tissue and is a major provider of circulating free fatty acids (FFA) to the liver and other tissues. Dysregulation of SAT is believed to be detrimental and contributes to pathogenesis of MetS and its downstream consequences including T2DM and ASCVD. Studies have reported that increased adiposity results in insulin resistance (IR) and increased macrophages in SAT of patients with MetS.

CRP

CRP, a member of the pentraxin family of proteins, is secreted by hepatocytes, lymphocytes, alveolar macrophages, monocyte-derived macrophages and endothelial cells in atherosclerotic plaques in response to IL-6 and other inflammatory markers. It is considered as the prototypic downstream marker of inflammation. The interaction between CRP and Fc receptors promotes the release of proinflammatory cytokines in the inflammatory response.

Macrophage/monocyte function

MetS can be characterized by monocytes and tissue macrophages that are activated into the proinflammatory phenotype. This novel observation was first made by Natal et al. who demonstrated that monocyte CD40 expression was elevated along with increased interaction with CD40L in MetS patients compared to controls.

Role of PMNs in MetS

Despite their key role in mediating inflammation, neutrophils have received little attention in regard to MetS. Researchers have found that MetS is associated with alterations in hematopoietic progenitors. As neutrophils predominate during early stages of inflammation, they lead to a significant cascade of events such as tissue infiltration by macrophages.

Metabolomics and inflammation in MetS

Multiple investigations have established a connection between inflammation and changes in metabolites including amines, amino acids, and lipids in the setting of MetS. Recent studies have further elucidated the role of these metabolites in the development, screening, and treatment of MetS as well as their contribution to the chronic, low-grade inflammatory state in MetS.

Role of Visceral Adiposity in Metabolic Syndrome

Visceral adiposity is the major risk factor responsible for the development of insulin resistance and the common pathophysiologic link to MetS. The pathophysiology of MetS is related to a diet containing excess calories and/or high saturated fat or glucose content and physical inactivity. Triacylglycerols provide the major source of energy which is used by skeletal muscle. They are comprised of a glycerol backbone in which each of the 3 hydroxyl groups is esterified with a fatty acid (7). The function of white adipose tissue is to store excess energy as TGs and then lipolyze and release free fatty acids (FFAs) into the circulation for use as energy in muscle. When nutrient intake exceeds the metabolic demand for energy, the excess TG is stored in adipocytes, liver and skeletal muscle. White adipose tissue is a highly active metabolic tissue which releases more than 50 different molecules known as adipocytokines, which regulate inflammation and immune function and the components of MetS including insulin sensitivity and blood pressure homeostasis as well as glucose and lipid metabolism (8). A second mechanism leading to insulin resistance results from actions of the FFAs lipolyzed from the stored TGs in adipocytes. FFAs function in signaling pathways to regulate glucose, fat and lipid metabolism and inflammation. FFAs can adversely affect insulin signaling and cause insulin resistance within adipocytes and in muscle and other tissues(9). Saturated fatty acids (SFAs) activate the Toll-like receptor (TLR) 4 signaling pathway indirectly through binding to Fetuin A, a circulating glycoprotein secreted from the liver. Fetuin A then binds to and activates TLR4. This induces activation of JNK and IKK which lead to serine phosphorylation of IRS-1 and inhibition of insulin signaling (10). JNK and IKK activation also leads to upregulation of NF-κB and AP-1 activation and thus production of inflammatory cytokines and defective insulin signaling (11). Activation of NF-κB upregulates VCAM1 on the endothelial cell to which monocytes attach and migrate into the subendothelial space where they are converted to macrophages which take up oxidized lipoproteins and form foam cells and the fatty streak (12,13). In support of these signaling events, TLR4-null mice do not develop insulin resistance or adipose inflammation when challenged with FFAs (14).

Vitamin D

Vitamin D is a fat-soluble prohormone that plays an essential role in bone mineral metabolism, being involved in calcium and phosphorus metabolism and skeletal homeostasis. The main source of vitamin D is cholecalciferol or vitamin D3, synthesized by sunlight on the skin from 7-dehydrocholesterol, for which cholesterol is a precursor (15). It is also available in the diet from animal (cholecalciferol) and vegetable (ergocalciferol) foods. Regardless of the source, vitamin D requires two hydroxylations in the organism to become biologically active, the first in the liver and the second in the kidney, resulting in the form known as 1,25(OH)2 vitamin D or calcitriol (16).

In the past, vitamin D was almost exclusively associated with bone health; however, numerous other functions have gradually emerged, and deficiency of this vitamin has been associated with a higher risk of certain autoimmune diseases (17). These extraskeletal actions are enabled by the presence of vitamin D receptors and hydroxylation enzymes in the cells of different human tissues and by differences in vitamin D production depending on the tissue in which it is expressed. Therefore, the fact that the vitamin D receptor and the enzyme 1α-hydroxylase are expressed in different tissues (kidney, pancreas, prostate, or immune system) shows the possible action of this vitamin on these tissues. Thus, changes in the expression of vitamin D receptors may be associated

with the development of MetS and its different components (18, 19, 20).

Vitamin D has also been attributed to hormonal activity, including endocrine, autocrine, and paracrine functions (21).

In addition to all these activities, vitamin D has other functions of pleiotropic nature such as its anti-inflammatory, anti-apoptotic and anti-fibrotic effects, preventive action against cardiovascular and renal diseases, diabetes mellitus, or cancer through different mechanisms of action widely described (22).

Interest in this vitamin has intensified over recent years due to the high prevalence of hypovitaminosis D, described as a worldwide epidemic (23).

Based on the levels of vitamin D, we can talk about insufficiency when 25(OH)D of 21–29 ng/mL, mild deficiency when levels are between 10 and 20 ng/mL, moderate deficiency between 9 and 5 ng/mL, and severe deficiency when vitamin D levels are lower than 5 ng/mL (24,25,26).

Meanwhile, the statements due to optimal level of Vitamin D 50-100 ng/mL have been discussing among family doctors, cardiologists, endocrinologists , dietologists.

The practical data shows that liver, intestine, kidneys, visceral obesity recovery strategies, in case of optimal vitamin D level, provides better results compare to normal (30-49 ng/mL) and deficiency levels.

Vitamin D and mental health

Vitamin D has immunomodulatory, neuroprotective, and neurotrophic properties and may affect the brain tissues involved in the pathophysiology of depression and anxiety. The results of studies in the literature on the relationship of vitamin D levels with supplementation, depression, and anxiety are inconsistent. It is thought that the reason for the inconsistency in studies examining vitamin D levels may be due to the use of different cut-off points regarding vitamin D adequacy, the differences in the groups in which the studies were conducted, and the differences in the tools used to determine depression and anxiety. It is thought that many factors may have contributed to the inconsistency in the studies in which vitamin D supplementation was evaluated, including the difference between the groups applied, the severity of depressive symptoms, the presence of comorbidities, initial 25(OH)D3 level, vitamin D supplement dose, supplement form, and duration. In addition, studies in the literature include not only individuals with symptoms of major depression or anxiety but also individuals with chronic inflammatory diseases such as ulcerative colitis, Crohn's, and diabetes. Therefore, positive outcomes in individuals with these diseases can be associated with the effect of vitamin D as an immunomodulator on metabolic and inflammatory markers. Although the cause and effect relationship of vitamin D with depression and anxiety has not been clarified in the literature, it is emphasized that low vitamin D levels cause an increase in the symptoms of these diseases. It is important to screen for vitamin D deficiencies regarding mood disorders, to plan appropriate treatments, and to determine the optimal dose. Therefore, the necessity of monitoring vitamin D levels in planned vitamin D supplements is also clear. Besides, vitamin D is not included in the guidelines in the literature on mood disorders. For this disease group, cohort studies are needed to determine the effectiveness of vitamin D levels, supplement dose, and form. (27)

Metabolic syndrome and mental stress

Stress activates the sympathoadrenal system and the hypothalamic-pituitary-adrenocortical (HPA) axis. Defense reactions involve catecholamine release, vagal withdrawal, cortisol secretion, and activation of the renin-angiotensin system; the less well characterized defeat reaction is a stimulus for cortisol production. (28, 29)

These mediators subserve functions that help the individual during short-term stress. When stress is frequent, adaptation (coping) is lacking, the ability to shut off the stress response is deficient, or the responses to stress are inadequate and compensatory mechanisms are activated, the allostatic load may become overwhelming and the adaptive processes become maladaptive (30).

Epidemiological studies have, nonetheless, shown associations between psychosocial factors and cardiovascular disease. (31)

The study by Brunner and coworkers (32) in this issue of Circulation examines the role of neuroendocrine activation in the metabolic syndrome and discusses the role of psychosocial factors and stress in this context.

MetS and Vitamin D Deficiency

Numerous authors have addressed the possible association between micronutrient deficiency and metabolic disorders, including MetS (33). Various pathophysiologic mechanisms have been proposed to underlie the effect of vitamin D on MetS components. One plausible explanation is that vitamin D affects insulin secretion and sensitivity, which play a key role in MetS development. The vitamin D receptor is expressed by β cells in the pancreas and in musculoskeletal and adipose tissues, among other peripheral tissues, and vitamin D deficiency can compromise the capacity of β cells to convert pro-insulin into insulin (34). Another pathophysiological mechanism could be related to the association between obesity and vitamin D deficiency. The two most accepted hypotheses are vitamin D sequestration and volumetric dilution. In the first case, this vitamin is sequestered in adipose tissue, increased in obese individuals, which also influences a greater volumetric dilution, according to which 25(OH)D, a fat-soluble molecule, would be distributed among fat, muscle, liver, and serum, decreasing serum vitamin D levels. Other possible explanations for this relationship described may be poor dietary habits, decreased sun exposure, the difference in gene expression in vitamin D metabolizing enzymes, and impaired hepatic 25-hydroxylation (35, 36).

A study of non-diabetic young people also showed an inverse relationship between vitamin D levels and the presence of MetS, attributed to the combined effect of obesity and IR (37). Lee et al. described a higher risk of MetS in Korean men and women aged over 65 years

with low 25(OH)D levels. After adjusting for age, area of residence, season, and habits (exercise, tobacco, and alcohol), there appeared a relationship between low vitamin D levels and increased prevalence of MetS, so the lower the vitamin D levels (14.20–18.99 ng/mL in men and 11.20–15.59 ng/mL in women) the higher the prevalence of elevated waist circumference, hypertriglyceridemia, and high low-density lipoprotein cholesterol (LDL) concentrations (38). Likewise, Zhu and Heil reported that 25(OH)D levels were inadequate in 50% of the study population, formed by residents of Shanghai, China, aged 19–70 years and were associated with the presence of MetS, observing a linear relationship between 25(OH)D concentrations and serum concentrations of glucose and lipids (39). They calculated that each increase of 1 ng/mL 25(OH)D was associated with a significant reduction in total cholesterol and LDL and a 54% decrease in the risk of MetS. Subsequent studies also reinforce the possible association between vitamin D deficiency and MetS prevalence (40, 41, 42).

Effect of Vitamin D Supplementation on MetS

Vitamin D supplementation has been reported to exert a beneficial effect in the treatment of MetS-related diseases, such as lipid profile, insulin resistance and hyperglycemia, obesity, and hypertension (43). This effect could be based on the mechanism of action of vitamin D on different physiological parameters, including improved arterial stiffness; decreased renin-angiotensin-aldosterone system activity, parathyroid hormone levels, inflammatory cytokines; increased activity of lipoprotein lipase; and improved phospholipid metabolism and mitochondrial oxidation (44).

Injectable VS Oral Vitamin D Supplementation

Optimizing vitamin D levels to normalize metabolism, digestive, excretory, and nervous systems requires 2 circumstances:

1. Sufficient intake of vitamin D with food.
2. The ability of the digestive tract to absorb vitamin D.

According to observations conducted at the "Institute of Spine and Joint Pathology named after Prof. M.I. Sytenko of the National Academy of Medical Sciences of Ukraine" (Kharkiv, Ukraine) in the period 2010-2024 (300 children aged 3 months to 18 years), oral correction of vitamin D levels among children leads to positive results within 3 months.

At the same time, during observations conducted in the SQLAB (experimental clinic, Kyiv, Ukraine) in 2016-2022 (500 patients), it was found that taking oral vitamin D among patients with metabolic syndrome without additional nutritional correction, adding co-factors to the diet, and treating gastrointestinal dysfunctions associated with metabolic syndrome did not yield the expected results in optimizing vitamin D levels.

The average time to optimize vitamin D levels in patients with metabolic syndrome took 6 months, included 4-8 consultations, 3-6 control tests for vitamin D, selection and replacement of various forms of oral vitamin D preparations. The costs for this were 400-600 USD.

At the same time, the use of injectable forms of cholecalciferol, which allowed vitamin D to be delivered to the blood via intramuscular injection, allowed to significantly increase its level in the blood 2-4 weeks after the first injection at a dose of 50,000-150,000 IU (depending on the patient's condition) significantly increase the level of vitamin D in the blood. This required only 2 consultations and 2 tests for the level of vitamin D. The costs were 100-200 USD.

This, in turn, led to improved results in the improvement of the digestive, circulatory, nervous, hormonal systems and musculoskeletal system.

Conclusions

A syndromic approach on the example of metabolic syndrome compared to the isolated treatment of its individual manifestations, including correction of nutrition (including parenteral), physical culture, and mental stress management, can be effective and deserves further study.

Optimizing vitamin D levels has a positive effect on the correction of metabolic and mental health indicators.

Vitamin D supplementation among children should be carried out by oral means.

Injectable vitamin D supplementation among patients with metabolic syndrome is optimal from both a clinical and economic point of view compared to oral means.

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